Delayed immune-related events after discontinuation of immunotherapy – DIRE syndrome?

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Delayed Immune-Related Events After Discontinuation of Immunotherapy – DIRE Syndrome?

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Background

Although the temporality of immune-related adverse events (irAE) during immunotherapy is well-recognized to be highly variable and often delayed,1,2 post-immunotherapy irAE are rarely described and potentially under-recognized. In 2013, two cases were reported in abstract form in Deutscher Dermatologischen Gesellschaft.[2] Since then, the number of published reports has steadily increased, more than doubling since January 2018. With increasing number of IO clinical trials in the curative neoadjuvant or adjuvant setting, larger numbers of patients will be exposed to IO in earlier stages of disease, often for limited courses. Given the potential for diagnostic misattribution in this setting, under-recognition of delayed immun-related events (DIRE) after completion of immunotherapy could pose a growing clinical hazard.

Methods

DIRE syndrome was defined as: newly diagnosed irAE ≥ 90 days post-immunotherapy discontinuation. We performed a literature review in PubMed between 1/1/2008 and 10/1/2018 (Figure 1) and included additional cases from our institution. Recrudescence irAE were excluded.

Results

We identified 25 cases (Table 1), 22 by literature review (16 melanoma, 5 NSCLC, 1 cutaneous SCC) and an additional 3 cases treated neoadjuvantly at our institution (3 HNSCC). Seventy-seven percent of cases (17/22) identified by literature review were in the recurrent/metastatic context, while twenty-three percent were adjuvant melanoma cases (5/22). Median interval from last immunotherapy dose to DIRE onset was 6 months (range: 3 to 28 months). Median cumulative immunotherapy exposure was 4 doses (range: 1 to 36 doses).

Conclusions

An influx of neoadjuvant clinical trial design over the last 2-3 years, incorporating brief IO exposure (typically checkpoint blockade) followed by surgical resection and/or adjuvant therapy in the curative setting, is attracting interest in multiple tumor types.[21-25] In this context, it will be necessary to recognize an emerging phenomenon, which we have termed DIRE syndrome (delayed immune-related events). Clinical vigilance has the potential to reduce morbidity, as these conditions are generally manageable with prompt diagnosis and initiation of treatment; or to avert unnecessary/harmful interventions due to misattribution (in the autoimmune meningitis case we report, an Ommaya reservoir was placed at an out-of-state hospital based on erroneous diagnosis of leptomeningeal carcinomatosis). Several confounding factors may contribute to misattribution following neoadjuvant IO: 1) subsequent standard of care treatments with potentially overlapping toxicity; 2) brief duration of IO exposure; 3) protracted process of diagnosis-by-exclusion. DIRE syndrome should therefore figure prominently in the differential diagnosis of new onset illness with unclear etiology, irrespective of post-immunotherapy interval.